REMARKS/ARGUMENTS

Claims 2-12 are pending in the present application. Claim 1 has been canceled without prejudice to or disclaimer of the subject matter contained therein. Applicants expressly reserve the right to file divisional applications or take such other appropriate measures deemed necessary to protect the inventions in this canceled claim. Claims 2, 4, and 5 have been amended. Specifically, claim 2 has been amended to recite that the intracellular or extracellular enzyme is "in or on an epithelial cell or surface." Support for this amendment may be found throughout the specification, for example, on page 15, lines 24-27. Claims 2, 4, and 5 have been amended to recite "wherein the targeting molecule does not contain at least one domain selected from the group consisting of the $C_H1\alpha$, $C_H2\alpha$, $C_H3\alpha$, and C_L domains." Support for this amendment may be found throughout the specification, for example, on page 8, lines 8-12. Claim 5 has further been amended to recite "wherein the imaging agent is not naturally linked with the targeting molecule." Support for this amendment may be found throughout the specification, for example, on page 19, lines 20-22. No new matter is added by way of claim amendment.

New Claims 7-12 have been added. Claims 7, and 9-11 are dependent claims specifying that the targeting molecule comprise at least Domain 2 of a J chain. Support for these claims may be found throughout the specification, for example, on page 11, lines 10-11. Claim 8 is directed towards a targeting molecule linked to at least one imaging agent, wherein said targeting molecule comprises a polypeptide that: (a) forms a closed covalent loop; and (b) contains at least three peptide domains having beta-sheet character, each of the domains being separated by domains lacking beta-sheet character, wherein the targeting molecule does not contain at least one domain selected from the group consisting of the $C_H1\alpha$, $C_H2\alpha$, $C_H3\alpha$, and C_L domains. Support for this claim may be found throughout the specification and in the original claims, for example, on page 2, lines 18-22, and on page 8, lines 8-12. Claim 12 is directed towards a targeting molecule capable of specifically binding to a basolateral epithelial surface and causing the internalization of an imaging agent linked thereto, wherein said targeting molecule consists of domain 2 of a J chain. Support for this claim may be found throughout the specification and in the original claims, for example, original claim 1, and on page 10, line 24, through page 11, line 11. No new matter is added by way of presentation of these new claims.

Claims 1-12 are now pending in the application. Reexamination and reconsideration of the claims is respectfully requested. The Examiner's remarks in the Office Action are addressed below in the order set forth therein.

The Rejection of the Claims under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

Claim 1 is rejected under 35 U.S.C. §112, first paragraph, as lacking an enabling disclosure. In order to further prosecution, claim 1 has been canceled. Therefore, the rejection of claim 1 is moot. It is respectfully submitted that the rejection should not be applied to new claims 7-12 for the reasons described below.

New claims 7-11 recite the structural features recited in claims 2, 4, and 5. New claim 12 requires that the polypeptide consist of Domain 2 of a J chain. Support for the amendment is found on page 11, lines 1-8 of the specification. Applicants have determined that Domain 2 is sufficient to provide targeting function. Therefore, the specification provides sufficient guidance to allow on of skill in the art to make and use the composition of claims 7 - 12.

The Rejection of the Claims under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 1-6 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed for the reasons described above.

Claim 1 has been rejected as being confusing and unclear by reciting "is not a full length dimeric IgA." In order to further prosecution, claim 1 has been canceled, thereby rendering this rejection moot.

Claim 2 has been rejected for reciting "an enzyme associated with an epithelial barrier." While Applicants do not agree that the meaning and scope of "associated" is uncertain, in order to further prosecution, claim 2 has been amended to recite "in or on an epithelial cell or surface." Support for this amendment may be found throughout the specification, for example, on page 15, lines 24-27. Applicants contend that this term clearly indicates that the enzyme is found inside the cell, or on the cell surface. One of skill in the art would understand the scope and meaning of this term. Therefore, the rejection of the claim should be withdrawn.

Claim 4 has been rejected for reciting "antibody combining site." The Examiner states that the meaning and scope are unclear. Applicants respectfully disagree. For example, the Glossary of Janeway et al. (2001) Immunobiology (5th ed., Garland Publishing, New York) defines this phrase as follows:

> The antigen-binding site of an antibody, or antibody combining site, is found at the surface of the antibody molecule that makes physical contact with the antigen. Antigen-binding sites are made up of six hypervariable loops, three from the light-chain V region and three from the heavy-chain V region.

Therefore, the term "antibody combining site" is clear and definite, and the rejection should be withdrawn.

Claim 5 has been rejected for reciting "not naturally associated with the targeting molecule." Although Applicants disagree with the Examiner that the term "associated with" is unclear, to further prosecution, the claim has been amended as suggested by the Examiner to recite "not naturally linked to the targeting molecule." Support for this amendment may be found throughout the specification, for example, on page 19, lines 20-22.

The Rejection of the Claims under 35 U.S.C. §102(b) Should Be Withdrawn

Claims 5 and 6 are rejected under 35 U.S.C. §102(b) as being anticipated by Terskikh *et al.* (1994) *Mol. Immunol.* 31:1313-1319. This rejection is respectfully traversed as applied to the amended claims for the reasons described below.

Claim 5 has been amended to recite a targeting molecule linked to at least one imaging agent, wherein the targeting molecule comprises a polypeptide that: (a) forms a closed covalent loop; and (b) contains at least three peptide domains having beta-sheet character, each of the domains being separated by domains lacking beta-sheet character; wherein the targeting molecule does not contain at least one domain selected from the group consisting of the $C_H1\alpha$, $C_H2\alpha$, $C_H3\alpha$, and C_L domains; and wherein the imaging agent is not naturally linked with the targeting molecule, and wherein the imaging agent is not iodine. Claim 6 depends from claim 5 and therefore contains all the limitations of claim 5.

Terskikh *et al.* disclose a dimeric IgA that can be radiolabeled for use in carcinoma localization. As the dimeric IgA used by Terskikh *et al.* contains a heavy chain containing contiguous variable $C_H1\alpha$, $C_H2\alpha$, and $C_H3\alpha$ domains, and a light chain containing contiguous variable and C_L domains (see Fig. 1 on page 1314), Terskikh *et al.* does not teach or suggest all the claim limitations. Therefore, the rejection of claims 5 and 6 as being anticipated by Terskikh *et al.* should be withdrawn.

The Rejection of the Claims under 35 U.S.C. §103(a) Should Be Withdrawn

Claims 2-6 are rejected under 35 U.S.C. §103(a) as being unpatentable over Terskikh *et al.* (1994) *Mol. Immunol.* 31:1313-1319 in view of Brandtzaeg and Baklien (1980) *Acta hisotchemica Suppl.* 21:105-119 and Anderson *et al.* (U.S. Patent No. 5,169,933), and if necessary in further view of Max and Korsmeyer (1985) *J. Exp. Med.* 161:832-849, Frutiger *et al.* (1992) *Biochemistry* 31:12643-12647, or Hendrickson *et al.* (1995) *J. Exp. Med.* 182:1905-1911. This rejection is respectfully traversed.

The current invention encompasses a targeting molecule linked to at least one imaging agent, wherein said targeting molecule comprises a polypeptide that: (a) forms a closed covalent loop; and (b) contains at least three peptide domains having beta-sheet character, each of the domains being separated by domains lacking beta-sheet character. Independent claims 2, 4, and 5 have been amended to require that the targeting molecule does not contain at least one domain selected from the group consisting of the $C_H1\alpha$, $C_H2\alpha$, $C_H3\alpha$, and C_L domains. Applicants have made the unexpected discovery that Domain 2 of a J chain is sufficient for targeting and causing the internalization of an imaging agent linked thereto.

Terskikh *et al.* disclose a dimeric IgA that can be radiolabeled for use in carcinoma localization. As the dimeric IgA used by Terskikh *et al.* contains a heavy chain containing contiguous variable $C_H1\alpha$, $C_H2\alpha$, and $C_H3\alpha$ domains, and a light chain containing contiguous variable and C_L domains (see Fig. 1 on page 1314), Terskikh *et al.* does not teach or suggest all the claim limitations.

Brandtzaeg and Baklien disclose that dimeric IgA containing a J chain is taken up by the columnar epithelial cells and selectively transported through the crypt epithelium. This reference

is directed towards the analysis of intestinal immunocyte populations associated with various bowel diseases. As with Terskikh *et al.*, Brandtzaeg and Baklien do not discuss molecules other than dimeric IgA that are selectively transported across epithelial cells. They do not teach or suggest that Domain 2 of J chain is sufficient to specifically bind and cause the internalization of an imaging agent linked thereto, as Applicants have. Therefore, Brandtzaeg and Baklien do not, alone or in combination with Terskikh *et al.*, teach or suggest all the claim limitations. To establish a prima facie case of obviousness (1) there must be some suggestion in the reference or knowledge generally available to one of ordinary skill in the art to modify the reference or combine the references; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. MPEP § 2143. Therefore, the Examiner has not established a prima facie case of obviousness.

Anderson *et al.* disclose covalently-linked complexes comprising a targeting protein, a cytotoxic agent, and an enhancing moiety, wherein the enhancing moiety is capable of promoting CLC-target cell interaction. In this patent, the targeting moiety is responsible for binding to a defined population of cells. The enhancing moiety is responsible for promoting membrane interaction, and can include translocating/internalizing moieties. This is distinguishable from the present invention, where the targeting molecule itself is responsible for the internalization of the linked imaging agent. In addition, none of the references, alone or in combination, teach or suggest the use of Domain 2 of a J chain.

Max and Korsmeyer, Frutiger *et al.* and Hendrickson *et al.* further disclose the nature of the J chain, but none of these references teach or suggest that a polypeptide that (a) forms a closed covalent loop; and (b) contains at least three peptide domains having beta-sheet character, each of the domains being separated by domains lacking beta-sheet character would be effective for specific binding and delivery through the epithelial surface of a linked imaging agent. Therefore, they do not, alone or in combination with Terskikh *et al.*, Brandtzaeg and Baklien, or Anderson *et al.* render the present invention obvious. Therefore, the rejection of claims 2-6 under 35 U.S.C. §103(a) should be withdrawn.

The Rejection of the Claims under 35 U.S.C. §103(a) Should Be Withdrawn

Claim 1 is rejected under 35 U.S.C. §103(a) as being unpatentable over Terskikh *et al.* (1994) *Mol. Immunol.* 31:1313-1319 in view of Brandtzaeg and Baklien (1980) *Acta hisotchemica Suppl.* 21:105-119 and Anderson *et al.* (U.S. Patent No. 5,169,933), and if necessary in further view of Max and Korsmeyer (1985) *J. Exp. Med.* 161:832-849, Frutiger *et al.* (1992) *Biochemistry* 31:12643-12647, or Hendrickson *et al.* (1995) *J. Exp. Med.* 182:1905-1911, and further in view of Carter *et al.* (U.S Patent No. 5,731,168). Claim 1 has been canceled in order to further prosecution, thereby rendering this rejection moot.

The Non-statutory Double-Patenting Rejection

Claims 1-6 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 6,391,280 or claims 1-37 of U.S. Patent No. 6,045,774. Upon notification of allowable subject matter in the present application, Applicants will file a terminal disclaimer compliant with 37 C.F.R. §1.130(b).

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §112, first and second paragraphs, §102(b), §103(a) and double patenting are overcome. Reconsideration and withdrawal of the rejections are therefore respectfully requested. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Kathryn L. Coulter

Kathryn L. Coulter
Registration No. 45,889

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

CERTIFICATE OF EXPRESS MAILING
"Express Mail" Mailing Label Number EV184328317US
Date of Deposit: January 28, 2005
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to MAIL STOP AMENDMENT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Nora C. Martinez

Nora C. Martinez